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(54) **Use of phytic acid or a salt thereof as an activator of hypoxic cells and a circulatory ameliorator.**

(57) Phytic acid or a salt thereof is known for pharmaceutical use. They are now administered orally as a treatment or preventive of hypoxic cells and dementia, and to improve blood circulation.

The phytic acid or salt may be contained in a food-stuff, confectionary or a liquid or pharmaceutical type of composition for oral use. The salts are used at pH 6 to 8.

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USE OF PHYTIC ACID OR A SALT THEREOF AS AN ACTIVATOR OF HYPOXIC CELLS AND A CIRCULATORY AMELIORATOR

The present invention relates to the use of pharmaceutical material for activating cells in a hypoxic state which contains, as an effective component, phytic acid or a salt thereof.

Thus, the compositions according to the present invention may be used as circulatory ameliorators and dementia remedies since, due to its erythrocytic oxygen dissociation function, phytic acid serves to activate cells in a hypoxic state, and may potentially be employed to treat and prevent various diseases attributed to the regression of circulatory functions, for instance, histionic cell dysfunctions such as cerebral circulation dysfunctions and cardiac tissue dysfunctions as well as frostbite and necrosis.

Pharmaceutical preparations based on xanthine, pyridine, nicotinic acid, rutin and vitamins have generally been used as circulatory ameliorators.

On the other hand, phytic acids widely appear in plants as calcium and magnesium salts, sometimes a potassium salt. For instance, rice bran contains as high as 9.5 to 14.5 % of phytic acid, and provides a starting material for commercial phytic acid and myoinositol derived therefrom.

Phytic acid and its salts have been used for many purposes; in pharmaceutical applications, calcium phytate has been used as a calcium enhancement, rice bran itself and sodium phytate as a preventive for calcium calculus and potassium phytate for the treatment of hyper-calcemia and hyper-calciurea of sarcoidosis patients. They have also been utilized in various other fields as fermentative aids for brewing saké and wine, metal removers making use of the chelating action of phytic acid, antioxidants in the presence of iron and calcium ions and anticorrosives for metals.

However, it has not been reported until now that phytic acid and salts thereof may be used a remedy and preventive for various diseases attributed to circulatory dysfunctions.

Surprisingly, the inventors have now discovered that when orally administer during nutrition experiments, phytic acid shows a detoxifying action and, moreover, serves to activate cells in a hypoxic state due to its erythrocytic oxygen dissociation function.

In view of the aforesaid findings, the present invention provide a pharmaceutical composition containing phytic acid or at least a salt thereof as an active component, which is used as a cell activator, circulatory ameliorator and dementia remedy in hypoxic conditions as well as an edible composition having such functions.

The pharmaceutical and edible compositions according to the present invention are administrable or applicable to both humans and animals.

In various preparations, phytates and their mixtures in a pH range of 6 to 8 may generally be selectively used depending upon the purposes of pharmaceutical and edible compositions because of their strong acidity.

The phytates usable in the present invention may include non-toxic metal salts as well as non-toxic salts with organic salts, basic amino acids and organic ester residues such as those represented by potassium phytate, sodium phytate, ammonium phytate, arginine phytate, ornithine phytate, lysine phytate, histidine phytate, monoethanolamine phytate, diethanolamine phytate, triethanolamine phytate and glucamine phytate.

The number of moles of various bases required to adjust one mole of phytic acid to pH 6 to 8 is shown in Table 1.

Table 1

Bases	pH:	6.00	7.00	8.00
NaOH		7.34	8.21	8.94
KOH		7.34	8.23	8.94
LiOH		7.41	8.38	9.30
NH_4OH		7.61	8.55	9.45
$HOC_2HCH_2NH_2$		7.72	8.68	9.52
$(HOCH_2CH_2)_2NH$		7.54	8.45	9.31
$(HOCH_2CH_2)_3N$		7.20	8.53	12.1
N-Methylglucamine		7.62	8.49	9.25
L-Arginine		7.79	8.67	9.60
L-Lysine		8.01	8.98	10.0
L-Histidine		11.3	-	-

In view of the actions and effects of diseases, there are diseases attributable to cerebral circulation dysfunctions, cardiac circulation dysfunctions and histionic circulation dysfunctions. More specifically, the cerebral circulation dysfunction diseases include dementia, amnesia, cerebral infarction, and the cardiac circulation dysfunction diseases include cardiac dysrhythmia and cardiovascular dysfunctions (angina pectoris). The histionic circulation dysfunction diseases include cold abcess, burns, frostbite and chilblains. The composition according to the present invention may be used as the remedies and preventives for such diseases, and may find use as the pre-treating agents and used to activate tissue during dermanaplasty.

When making the preparations of the present invention, phytic acid or salts thereof may be dissolved in water for direct use. However, they may be powderized with suitable excipients or vehicles, or may be granulated into granules, tablets, etc. and may further be formulated into medicines for external application.

Since phytic acid is a strong acid, it is preferred in view of the sense of taste, etc. that when the compositions of the present invention are prepared primarily for oral administration, various salts of phytic acid are adjusted to pH about 6 to 8 and selectively used alone or in combination as an active component depending upon the intended purposes.

According to the present invention, phytic acid or its salts may be administered by way of the oral route, since they are effective in the form of both liquid and solid.

Examples

The present invention will now be explained in further detail with reference to the following test and preparation examples.

Example 1 - Test Examples

1. Pharmaceutical with Pharmacological Effect Tests

Experimental Materials

(a) Experimental Animals

Use was made of ddy male mice of five-week age.

(b) Drug to be Examined and Their Preparation

Sodium phytate (Lot. M7K7653, Hani Kagaku) in amounts of 200 mg/kg, 100 mg/kg and 50 mg/kg was dissolved in a small amount of physiological saline, which was then regulated to pH about 7 with dilute hydrochloric acid (confirmed by pH-paper). The solutions were diluted to the respective concentrations of 20 mg/ml, 10 mg/ml and 5 mg/ml with physiological saline and intraperitoneally administer to the animals in an amount of 10 ml/kg. Intraperitoneally administered to a control group were 10 ml/kg of physiological saline.

Effective Test 1 - Defensive Action upon Mice under Hypoxic Load

Due to its promoted erythrocytic oxygen dissociation function, phytic acid is expected to produce a defensive action upon various disorders in a hypoxic state. Accordingly, the mice were allowed to inhale carbon dioxide gas to determine its influence upon their survival time.

Experimental Procedures

Sixty (60) minutes after the intraperitoneal administration of the drug to be examined, the animals were placed in a desiccator (of 19 cm in diameter and 20 cm in height), and carbon dioxide gas was then injected thereinto to measure the length of time for the animals to die. It is noted that 30 minutes or 60 minutes after administration, the test and control groups, each of four mice, were simultaneously placed in the desiccators.

In the statistical assay carried out according to the Student's t-test method, the average ± the standard deviation was calculated for each group.

Results and Considerations

The results of the respective groups are set out in Table 2.

When CO_2 was loaded 30 minutes after administration, there was an increase in the survival time of the test groups to which 50 mg/kg, 100 mg/kg and 200 mg/kg of phytic acid were administered as compared with the control group, but such an increase was insignificant. When CO_2 was loaded 60 minutes after administration, on the other hand, there was no difference in the survival time between the control group and the test groups to which 50 mg/kg and 100 mg/kg of phytic acid were administered but there was a significant increase ($p<0.01$) in the survival time of the test group to which 200 mg/kg of phytic acid were administered.

As discussed above, it has been found that when CO_2 is loaded 30 minutes after the administration of phytic acid, no influence is produced upon the survival time, but the survival time is noticeably increased when CO_2 is loaded 60 minutes after the administration. Thus, phytic acid has been found to activate cells in a hypoxic state and produce a defensive effect upon hypoxic disorders.

Table 2

Action of Phytic Acid upon Survival Time under Hypoxic Load (Inhalation of CO_2)				
	Dosage (mg/kg i.p.)	n	weight (g)	Survival Time (sec)
30 Min after Administration				
Control Group	10	7	29.2±0.21	385.8±27.34
Test Group	50	7	29.7±0.40	474.4±45.8
"	100	7	29.1±0.21	478.3±48.01
"	200	7	29.7±0.13	455.7±76.59
60 Min after Administration				
Control Group	10	10	25.6±0.32	372.7±18.82
Test Group	50	10	26.0±0.42	376.1±16.33
"	100	10	26.2±0.29	377.4±21.40
"	200	10	25.9±0.66	556.4±55.36**

**p<0.01 vs control (Student t-test)

Effect Test 2 - Action upon Erythrodegeneration of Mice

In order to clarify how phytic acid, now known to have an erythrocytic oxygen dissociation function, acts upon erythrodegeneration, tests were carried out in vitro with the red blood cells of rats according to the filtration pressure method.

Experimental Procedures

An erythrocytic suspension was incubated at 37 °C for 5 minutes and then cooled down to room temperature. With a sustended injector (of the 2ch type, manufactured by Natsume Seisakusho), the suspension was passed at a rate of 5 ml/min through a Millibore membrane (SMWP 013 00, Lot No. N7BU008, manufactured by Millibore) having an average diameter of 5 μm to record its upstream side pressure on recording paper through a pressure transducer (TP-200TL, manufactured by Nippon Koden).

The filtration pressure was estimated in terms of a pressure increase per min until the lapse of 8 minutes from the commencement of injection, and erythrodegeneration was taken as being influenced when there was a significant difference between the control and test groups, as estimated according to the Student's t-test method.

Phytic acid (in the form of a sodium salt, Lot No. M7K7653, manufactured by Hani Kagaku) was dissolved in physiological saline and regulated to pH 7.0 with hydrochloric acid. Used as the control was physiological saline containing no phytic acid.

Hemolysis

Fifty (50) μl of red blood cells prepared in a similar manner as mentioned above were dissolved in a solution of phytic acid in physiological saline to prepare 5 ml of an erythrocytic suspension containing 1 % of phytic acid. The suspension was incubated at 37° C for 5 minutes and then centrifuged at 3,000 rpm for 10 minutes. The absorbance of the supernatant was measured at 540 nm to presume the content of free

hemoglobin.

The dissolution of phytic acid and the control were the same as mentioned above.

Test Results

1. Action upon Erythrodegeneration

As set out in Table 3, no appreciable filtration pressure drop was found at 1 mM of phytic acid (at the final concentration), but a filtration pressure rise was about one half of that of the control group, indicating a significant ($p<0.01$) drop.

2. Hemolysis

As set out in Table 4, even when the (final) concentration of phytic acid was 5 mM, there was no difference in the absorbance of the supernatant fluids between the test and control groups, indicating no sign of hemolysis.

Considerations

Human red blood cells are each in the form of a disc which is about 8 μm in diameter and thinner in its central region (i.e. biconcave), and are known to circulate through capillary vessels in varied forms. Accordingly as one way for helping to facilitate the circulation of the blood through histionic circulation regions, esp., microhistionic circulation regions, pentoxifylline has primarily been proposed to enhance erythrodegeneration. Experimentally, the blood may be sucked up through a capillary pipette to count the number of red blood cells contained therein. Alternatively, it is proposed to measure filtration pressure or count the number of red blood cells filtered through a membrane including bores each smaller in size than a red blood cell. In the present testing, the most general and simplest filtration pressure method was used.

As already referred to in the "Test Results", the filtration pressure dropped remarkably when the concentration of phytic acid was 5 mM. This was considered to result from promoted erythrodegeneration, rather than from hemolysis.

Thus, it has been found that phytic acid serves to promote not only the erythrocytic oxygen dissociation function but also erythrodegeneration. This suggests a possibility of transferring oxygen into tissue as well as a possibility of ameliorating microcirculation, particularly, ischaemic conditions.

Table 3

Action of Phytic Acid upon Erythrodegeneration of Mice			
Drug	Concentration	n	Filtration Pressure (mmHg/min)
Control Group		6	12.4±0.6
Test Group	1 mM	3	10.1±0.3
"	5 mM	3	6.0±0.6""

"": $p<0.01$, compared with the control.

Table 4

Hemolysis by Phytic Acid			
Drug	Concentration	n	O. D. (540nm)
Control Group		3	0.026±0.006
Test Group	1 mM	3	0.035±0.002
"	5 mM	3	0.039±0.003

Effect Test Example 3 - Action upon Mouse's Amnesia

Due to its promoted erythrocytic oxygen dissociation function, phytic acid is expected to produce a defensive effect upon various disorders. Such as defensive effect was studied with a dysmnesia model induced by the loading of a carbon dioxide gas.

Experimental Procedures

The indication used was a single passive avoidance reaction.

1) Acquisition Trial

An animal was placed in the bright chamber of a bright and dark box (comprising a bright chamber and a dark chamber, both being of 15.0 x 17.5 x 18.5 cm and including an inlet/outlet combination of 6.0 x 6.0 cm to measure the length of time before the animal walked into the dark chamber (the reaction potential time during acquisition, hereinafter abbreviated as A.T.). From just after the animal walked into the dark chamber, foot shocks of 2.5 mA were continuously applied to the animal through a floor grid with a shock generator scrambler, manufactured by Astech Co., Ltd., until the animal again walked into the bright chamber. To confirm that the model was obtained, no foot shock was applied to a control group (no-FS + hypoxia).

2) Retention Trial

After 24 hours of the acquisition trial, the animal was again placed in the bright chamber of the bright/dark box to measure the length of time before the animal walked into the dark chamber (the reaction potential time during the retention trial, hereinafter abbreviated as R.T.).

3) Preparation of Dysmnesia Model

Immediately after the acquisition trial, the animal was placed in a desiccator of 19 cm in diameter and 20 cm in height, and a CO_2 gas was then injected into the desiccator for 40 to 45 seconds till apnoea. After the animal was removed from the desiccator, artificial aspiration was immediatelytried thereon. The animal was then put back in a home cage. For the confirmation of the model, no CO_2 was injected into the dessicator for a control group (FS + no-hypoxia).

4) Administration of Drug

The drug to be examined was intraperitoneally administered to a test group of animals at a dosage of 10 ml/kg 30 minutes or 60 minutes before the acquisition trial, while 10 ml/kg of physiological saline was

intraperitoneally administered to a control group of animals.

5) Statistical Assay

For the animals having R.T. exceeding 360 seconds, the average ± the standard deviation was found for each group assuming that R.T. was 360 seconds, and statistical assay was carried out according to the Student's t-test method. For the animals having R.T. exceeding 360 seconds, on the other hand, the retention % was calculated assuming that the memory was retained, and both-side assay was made according to the Fisher's exact probability method.

Results and Considerations

The results of the respective groups are set out in Table 5.

Referring to the groups of animals to which phytic acid was administer 30 minutes before the acquisition trial, there was no difference in the reaction potential time (A.T.) during the acquisition trial between the control group and the test group to which 50 mg/kg of phytic acid was administered. However, there was a significant increase in the reaction potential time between the control group and the test groups to which 100 mg/kg and 200 mg/kg of phytic acid was administered, but that increase was of no significance. Referring on the other hand to the groups to which phytic acid was administered before 60 minutes of the acquisition trial, there was no difference between the control group and the test groups to which 50 mg/kg, 100 mg/kg and 200 mg/kg of phytic acid was administered. The FS + no-hypoxia control was 64.8 ± 11.1 seconds, while the no-hypoxia control was 44.5 ± 9.1 seconds. In the group to which phytic acid was administered 30 minutes before the acquisition trial, an increase in A.T. was found at a dosage of 100 mg/kg or more but, in the groups to which phytic acid was administered 60 minutes before, such an increase was not found. After about 30 minutes from the administration, phytic acid had some influence upon the behavior of the animals, but such influence was lost after 60 minutes.

Turning to the groups to which phytic acid was administered 30 minutes before the acquisition trial, there was no difference in the reaction potential time (R.T.) during the retention trial between the control group and the test groups to which 50 mg/kg and 100 mg/kg of phytic acid were administered. Referring to the groups to which phytic acid was administered 60 minutes before the retention trial, there was a significant increase ($p<0.05$) between the control group and the test groups to which 50 mg/kg and 100 mg/kg of phytic acid were administered, but no difference was found in the test group to which 200 mg/kg of phytic acid was administered. In the groups to which phytic acid was administered before 30 minutes, no amelioration of dysmnesia was found at any dosage. Thus, the influence of phytic acid upon the behavior of the animals during the acquisition trial were considered to take part in R.T. In the groups to which phytic acid was administered 60 minutes before, noticeable amelioration of dysmnesia was found at the dosages of 50 mg/kg and 100 mg/kg, but any amelioration of dysmnesia was not found at the dosage of 200 mg/kg. This implies that phytic acid acts in the Belshave's form.

Due to its promoted erythrocytic oxygen dissociation function, phytic acid serves to enhance the transfer of oxygen into anoxic regions and so treat histionic disorders due to anoxia. Indeed, phytic acid was found to have an effect upon the amelioration of dysmnesia. It is thus suggested that the promoted erythrocytic oxygen dissociation function is effective for dysmnesia due to hypoxic disorders.

Table 5

Action of Phytic Acid upon Dysmnesia due to the Inhalation of Carbon Dioxide					
	Dosage (mg/kg i.p.)	n	A.T.(sec)	R.T. (sec)	R (%)
30 Min beforehand					
Control Group	10	15	37.5±4.9	185.0±26.5	13
Test Group	50	18	38.5±4.6	182,9±25.7	22
"	100	20	8.78±12.4***	205.0±26.1	25
"	200	17	114.8±22.9**	136.5±30.3	17
60 min beforehand					
Control Group	10	28	51.8±9.1	189.4±19.2	17
Test Group	50	24	44.6±6.5	255.1±19.4*	33
"	100	26	50.5±5.7	258.2±20.6*	38
"	200	23	61.3±8.2	204.2±23.7	21
Foot Shock + No-Hypoxia		14	68.4±11.1	360.0±0.0***	92 + + +
No-Foot Shock + Hypoxia		13	44.5±9.1	50.6±19.7***	0 + + +
*p<0.05, **p<0.01, ***p<0.001 vs its control (Student's t-test), + + +p<0.001 vs its control (Fisher's exact probability test).					

2: Taste Testing

One hundred and eighty (180)-milliliter shots of saké and whisky-and-water containing 0.5 g (100 mg calculated as phytic acid) of the liquid preparation according to Preparation Example 4 were simultaneously provided to two 20-member panels to carry out taste testing for comparing both the shots in terms of whether taste and smell are good or bad. The results are set forth in the following table.

	Indistinguishable from Phytic Acid-Free Shots	Better than Phytic Acid-Free Shots	Bad
Taste	14	6	0
Smell	18	2	0

From the above results, it has been found that the preparation according to the present invention tastes good, and is effective as a liquor additive.

Example 2

Composition a

Twenty-nine (29) g of sodium hydroxide and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition b

Four hundred and twelve (412) g of potassium hydroxide and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition c

One hundred and seventy-seven (177)g of lithium hydroxide and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition d

Five hundred and eighty-one (581) g of ethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition e

Nine hundred and seventy-nine (979) g of diethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition f

One thousand eight hundred and five (1805) g of triethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition g

One thousand six hundred and fifty-seven (1657) g of N-methylglucamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 7.

Composition h

One thousand five hundred and ten (1510) g of L-arginine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 7.

Composition i

One thousand seven hundred and fifty-three (1753) g of L-histidine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition j

One hundred and sixteen (116) g of sodium hydroxide, 478 g of potassium hydroxide, 6.08 g of potassium chloride (as a dihydrate), 157 g of disodium hydrogen phosphate (as an anhydride) and a

suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 9.

These compositions a to j may be powdered by crystallization or the addition of a vehicle.

These compositions a to j may also be formed into compositions in the form of liquids or powders, from which the preparations may be obtained.

Example 3

The composition j obtained in Example 2 was formed into compositions below, from which various preparations were obtained.

Composition A for Preparations

Lactose is added to the composition j (containing 200 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition B for Preparations

Lactose is added to the composition j (containing 100 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition C for Preparations

Refined water is added to the composition j (containing 100 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition D

Light silicic anhydride is added to the composition j (containing 200 mg of phytic acid), followed by drying, which gives a total of 1000 mg of a composition.

Production Examples of Preparations

Production Example 1 (Elixir)

Composition C	100 g	(10 g calculated as phytic acid)
Compound orange extract	24 ml	
Ethanol	400 ml	
Glycerine	400 ml	
Refined water Total:	1000 ml	

Predetermined amounts of the aforesaid components are uniformly mixed together to obtain a colorless and clear elixir preparation. A five-milliliter dosage of this elixir preparation contains 50 mg of phytic acid.

Production Example 2 (Capsule)

Composition A	200 mg	(40 mg calculated as phytic acid)
Lactose	20 mg	
Corn starch	38 mg	
Magnesium stearate	2 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together and packed in No. 2 capsules. One such capsule contains 40 mg of phytic acid.

Production Example 3 (Granule)

Composition A	600 mg	(120 mg calculated as phytic acid)
Lactose	140 mg	
Corn starch	250 mg	
Hydroxypropylcellulose	10 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together, and the mixture is then wet-granulated with water and ethanol into granules. One hundred and twenty (120) mg of phytic acid are contained in an one-gram dosage of such granules.

Production Example 4 (Powder)

The composition A is divided and heat-sealed in aluminium to obtain wrappers each of 1.5 g of powder.

Production Example 5 (Tablet)

Composition A	100 mg	(20 mg calculated as phytic acid)
Corn starch	19 mg	
Crystalline cellulose	30 mg	
Magnesium stearate	1 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together, and the mixture is then compressed into tablets each of 7 mm in diameter and 150 mg in weight. One such tablet contains 20 mg of phytic acid.

Production Example 6 (Syrup)

Composition C	50 g	(5 g calculated as phytic acid)
White sugar	300 g	
D-sorbitol(70%)	250 g	
Methyl p-oxybenzoate	0.3 g	
Propyl p-oxybenzoate	0.15 g	
Sodium citrate	10 g	
Perfume	1.5 g	
Refined water Total:	1000 ml	

Predetermined amounts of the aforesaid components are dissolved and mixed together into a colorless and clear syrup. One hundred (100) mg of phytic acid is contained in a twenty-milliliter dosage of this syrup.

Production Example 7 (Dry syrup)

Composition B	100 mg	(10 mg calculated as phytic acid)
Sodium citrate	2.4 mg	
Citric anhydride	2.2 mg	
Tragacanth powders	2.7 g	
White sugar	suitable amount	
Hydroxypropylcellulose	3.0 mg	
Perfume	slight amount	
Perfume	slight amount	

Predetermined amounts of the aforementioned components are uniformly mixed together, and are then wet-granulated with water and ethanol into a dry syrup. A one (1)-gram dosage of this syrup contains 10mg of phytic acid.

Production Example 8 (Troche)

Composition A	100 mg	(20 mg calculated as phytic acid)
White sugar	870 mg	
Lactose	20 mg	
Magnesium stearate	10 mg	

Of the aforesaid components the composition A and white sugar are uniformly mixed together in the respective amounts of 100 g and 870 g, and are then wet-granulated with water and ethanol, followed by drying at a temperature of lower than 35° C. Added to the dried product are 20 g of lactose and 10 g of magnesium stearate to obtain troches each of 15 mm in diameter and 1 g in weight. One such troche contains 20 mg of phytic acid.

Production Example 9 (Candy)

Composition B	100 mg	(10 mg calcuated as phytic acid)
White sugar	2400 mg	
Starch syrup	1500 mg	
Perfume	slight amount	

Of the aforesaid components, 240 g of white sugar and 150 g of starch syrup are mixed with 100 g of refined water. After melting by heating, the mixture is sieved for the removal of foreign matters. The resulting liquid is concentrated under pressure with the application of heat for dehydration to prepare a starch syrup dough having a moisture content of 2 to 3 % at 130 to 150°C. Added to this dough are 10 g of the composition B and a slight amount of perfume, and the product is molded to obtain candies each of 4 g in weight. Each candy contains 10 mg of phytic acid.

Production Example 10 (Magnesium Citrate Oral Solution)

Composition C	3 g	(300 mg calculated as phytic acid)
Syrup	2.5 ml	
Refined water Total:	30 ml	

Predetermined amounts of the aforesaid components are uniformly mixed together into "limonda". A thirty (30)-milliliter dosage of such limonadas contains 300 mg of phytic acid.

Production Example 11 (Granule)

Composition D	500 mg	(100 mg calculated as phytic acid)
Garlic powders	750 mg	
Lactose	suitable amount	

Predetermined amounts of the aforesaid components are uniformly mixed together, and are then wet-granulated with water and ethanol into granules. One hundred (100) mg of phytic acid is contained in an 1.5-gram dosage of such granules.

Production Example 12 (Drinkable Solution)

Composition C	1 g	(100 mg calculated as phytic acid)
Mel	0.5 g	
White sugar	2.0 g	
Citric acid	suitable amount	
Sodium citrate	suitable amount	
Peppermint	slight amount	
Refined water	suitable amount	

Predetermined amounts of the aforesaid components were uniformly mixed together into a colorless and clear internal liquid preparation. A thirty (30)-milliliter dosage of this liquid preparation contains 100 mg of phytic acid.

Production Example 13 (Garlic Flavoring)

Composition D	0.285 g	(0.1 g calculated as phytic acid)
Avicel (Cellulose microcrystalline)	0.18 g	
Garlic powders	0.75 g	
Light silicic anhydride	0.256 g	
Corn starch	suitable amounts	

Predetermined amounts of the aforesaid components are granulated by a conventional method.

Production Example 14 (External Application O/W Ointment)

Sodium Phytate	0.5 %
Liquid Paraffin	10.5 %
Butylene Glycol	5.0 %
Beeswax	2.0 %
Cetyl Alcohol	4.0 %
Lanolin	2.0 %
Squalane	30.0 %
Paraben	0.2 %
Polyoxyethylene Monosorbitan Laurate	2.0 %
Water	Balance

The above components were blended together at the specified proportions to prepare an ointment.

Stability Testing

The preparations according to Production Examples 1 to 12 were subjected to stability testing to measure the amount of residual phytic acid. The results are set forth in Table 6.

Table 6

Amounts of Residual Phytic Acid in the Stability Testing of the Preparations According to the Production Examples (% with respect to the specified contents)			
Samples	Storage Vessels	At the beginning of Storage	After 3 weeks at 60° C
P.Ex.1A*	Glass Bottle	100.5	101.2
P.Ex.2B*	PTP	101.4	99.4
P.Ex.3C*	Aluminium Wrapper	100.1	100.0
P.Ex.4D*	"	100.9	102.1
P.Ex.5E*	PTP	99.2	99.8
P.Ex.6F*	Glass Bottle	102.1	100.3
P.Ex.7G*	Aluminium Wrapper	100.6	100.1
P.Ex.8H*	Aluminium SP	99.7	100.5
P.Ex.9I*	Aluminium Bag	99.9	99.2
P.Ex.10J*	Glass Bottle	102.1	100.9
P.Ex.11K*	Aluminium Wrapper	100.3	100.1
P.Ex.12L*	Glass Bottle	100.1	99.8
A*: Elixir, B*: Capsule, C*: Granule, D*: Powder, E*: Tablet, F*: Syrup, G*: Dry Syrup, H*: Troche, I*: Candy, J*: Limonada, K*: Granule, L*: Drinkable Solution.			

Claims

1. Use of phytic acid and/or a salt thereof for the manufacture of a medicament for activating hypoxic cells.

2. Use of phytic acid and/or a salt thereof for the manufacture of a medicament for improving blood circulation.

3. Use of phytic acid and/or a salt thereof for the manufacture of a medicament for treating or preventing dementia.

4. Use as claimed in any preceding Claim, wherein the salt of phytic acid is a non-toxic metal salt or a non-toxic salt with an organic base, a basic amino acid or an organic ester residue.

5. Use as claimed in Claim 4, wherein the salt of phytic acid is selected from potassium phytate, sodium phytate, ammonium phytate, orginine phytate, ornithine phytate, lysine phytate, histidine phytate, monoethanolamine phytate, diethanolamino phytate, diethanoamine phytate, triethanolamine phytate and glucamine phytate.

6. A medicament as claimed in any of the preceding Claims in a form suitable for oral administration.

FIG. 1

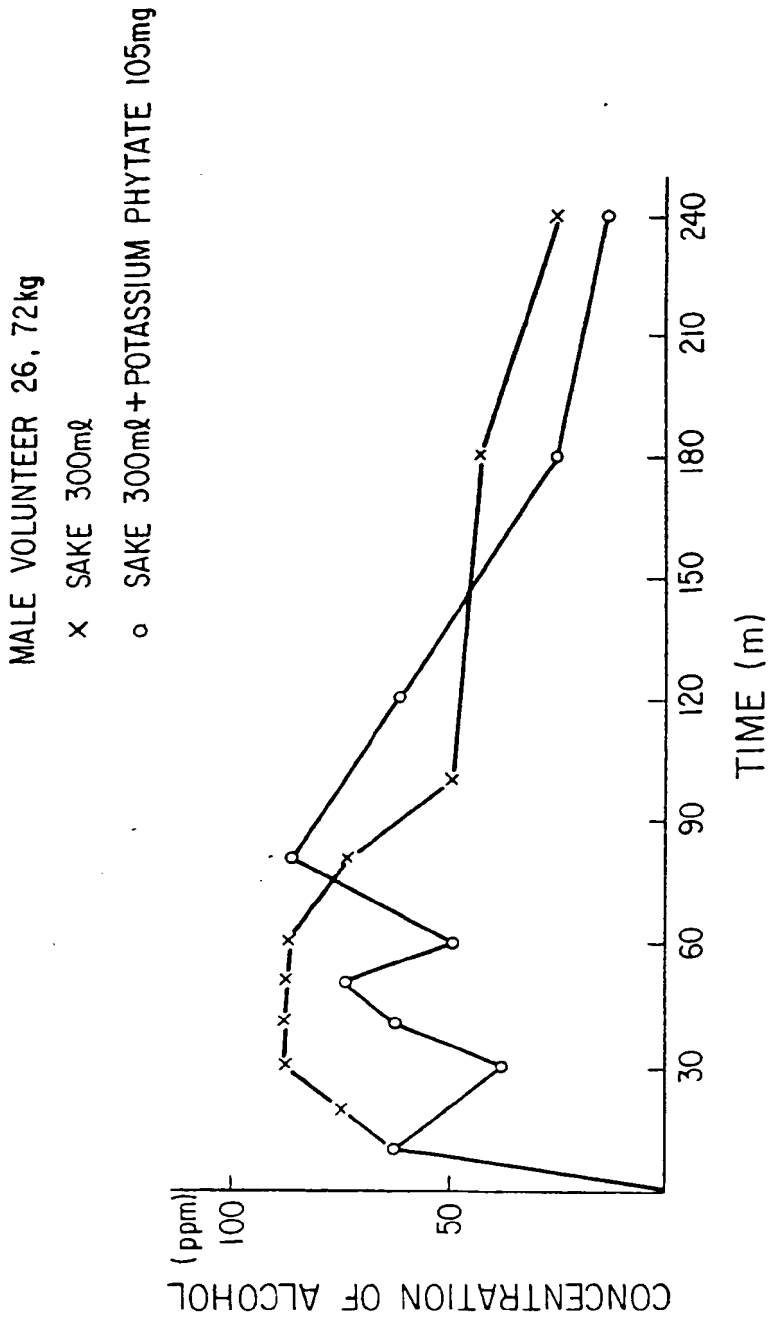

MALE VOLUNTEER 26, 72kg
× SAKE 300mℓ
o SAKE 300mℓ + POTASSIUM PHYTATE 105mg
CONCENTRATION OF ALCOHOL (ppm)
100
50
30
60
90
120
150
180
210
240
TIME (m)

FIG. 2

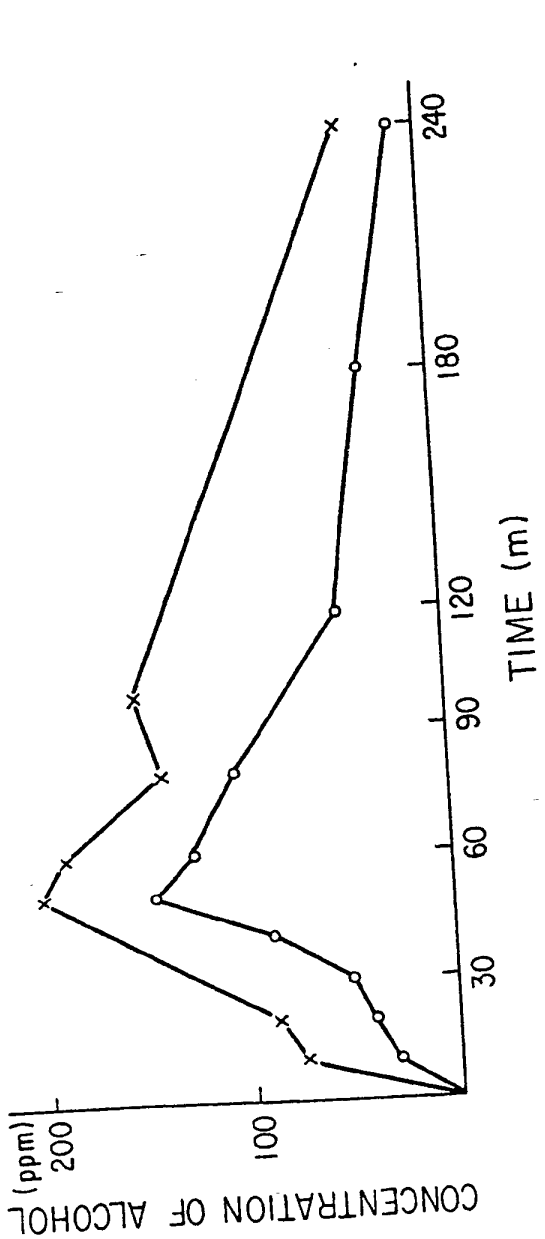
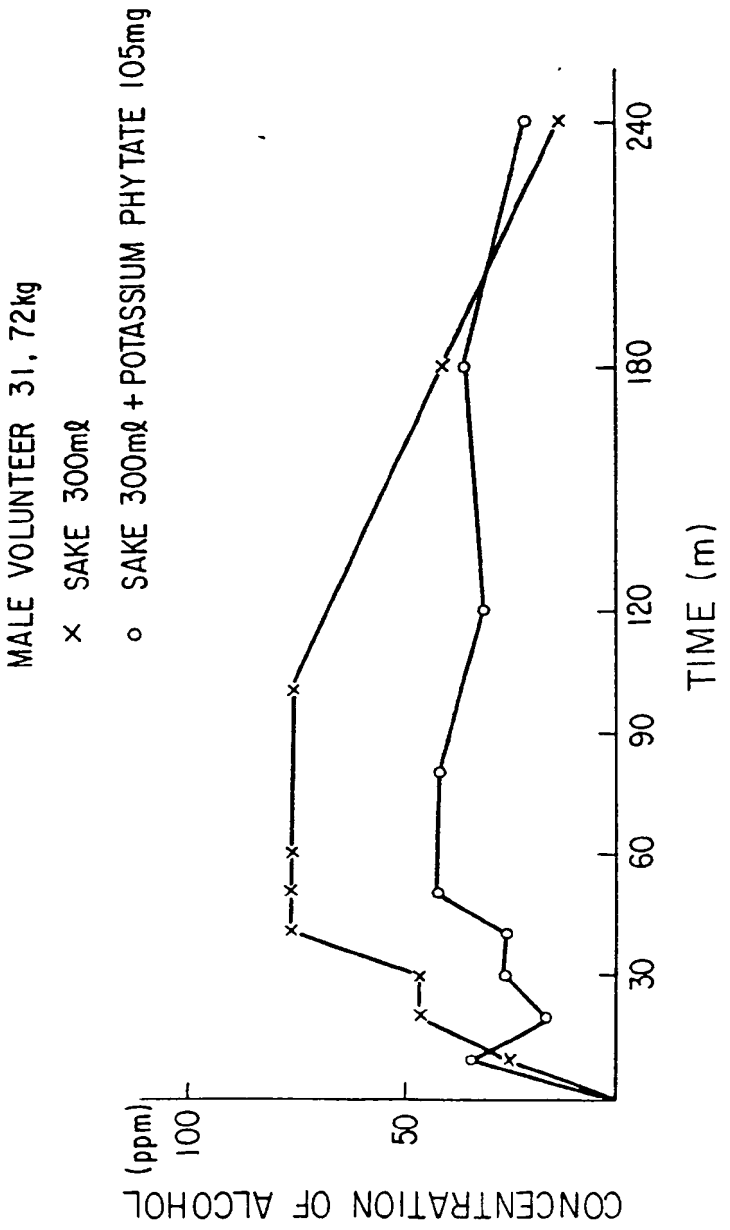

MALE VOLUNTEER 27, 56kg
× SAKE 300mℓ
○ SAKE 300mℓ + POTASSIUM PHYTATE 105mg
CONCENTRATION OF ALCOHOL (ppm)
200
100
30
60
90
120
180
240
TIME (m)

FIG. 3


MALE VOLUNTEER 31, 72kg
× SAKE 300mℓ
○ SAKE 300mℓ + POTASSIUM PHYTATE 105mg
CONCENTRATION OF ALCOHOL (ppm)
100
50
30
60
90
120
180
240
TIME (m)

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(54) **Use of phytic acid or a salt thereof as an activator of hypoxic cells and a circulatory ameliorator.**

(57) Phytic acid or a salt thereof is known for pharmaceutical use. They are now administered orally as a treatment or preventive of hypoxic cells and dementia, and to improve blood circulation.

The phytic acid or salt may be contained in a food-stuff, confectionary or a liquid or pharmaceutical type of composition for oral use. The salts are used at pH 6 to 8.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 5392

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	US-A-4 473 563 (NICOLAU et al.) * Column 1, lines 54-59; column 2, lines 39-43; column 12, line 52 - column 14, line 7 *	1-6	A 61 K 31/66
Y	XIITH ANNUAL MEETING OF THE EUROPEAN SOCIETY FOR ARTIFICIAL ORGANS, Athens, 16th - 19th September 1985, LIFE SUPPORT. SYST. 3 (Supp 1), 1986, (RECD 1987), pages 458-461; O. STUCKER et al.: "Incorporation of inositol hexaphosphate in stored erythrocytes: Effect on tissue oxygenation" * Page 460, lines 6-8,12-17 *	1-6	
Y	BIOCHIM. BIOPHYS. ACTA, vol. 236, 1971, pages 211-221; K. RUCKPAUL et al.: "Interaction of hemoglobin with ions allosteric effects of the binding of anions" * Page 215, lines 3-8 *	1-6	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	JOURNAL OF COMPARATIVE PHYSIOLOGY B, vol. 128, 1978, pages 127-137, Springer-Verlag; R.E. WEBER et al.: "Respiratory adaptations in carp blood influences of hypoxia, red cell organic phosphated, divalent cations and CO2 on hemoglobin-oxygen affinity" * Page 127, right-hand column, lines 21-28; page 130, right-hand column, lines 21-30; page 132, figure 5 *	1-6	A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	16-07-1990	GERLI P.F.M.

CATEGORY OF CITED DOCUMENTS

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